DIHYDROOXADIAZINONES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is the U.S. national phase application, pursuant to 35 U.S.C. § 371, of PCT International Application Serial No.: PCT/EP2018/071039, filed Aug. 2, 2018, which claims the benefit of and priority to U.S. Provisional Application No. 62/541,627, filed Aug. 4, 2017, the entire contents of each of which are incorporated herein by reference.

[0002] The present invention provides dihydrooxadiazinone compounds of general formula (I) as described and defined herein, methods of preparing said compounds, pharmaceutical compositions and the use of said compounds for the treatment or prophylaxis of diseases, in particular of hyperproliferative diseases.

BACKGROUND

[0003] Cancer kills over 550,000 people in the United States and over 8 million people world-wide each year. New agents, including small molecules, molecules that impact tissue-specific growth requirements, and immunomodulatory agents, have been shown to benefit a subset of patients whose cancers have unique genomic mutations or other characteristics. Unfortunately, many cancer patients are still left without effective therapeutic options.

[0004] One approach to identify new anti-cancer agents is phenotypic screening to discover novel small molecules displaying strong selectivity between cancer cell lines, followed by predictive chemogenomics to identify the cell features associated with drug response. In the 1990s, Weinstein and colleagues demonstrated that the cytotoxic profile of a compound can be used to identify cellular characteristics, such as gene-expression profiles and DNA copy number, which correlate with drug sensitivity. The ability to identify the features of cancer cell lines that mediate their response to small molecules has strongly increased in recent years with automated high-throughput chemosensitivity testing of large panels of cell lines coupled with comprehensive genomic and phenotypic characterization of the cell lines. Phenotypic observations of small molecule sensitivity can be linked to expression patterns or somatic alterations, as in the case of trastuzumab-sensitive HER2-amplified breast cancer or erlotinib-sensitive EGFR-mutant lung cancer.

[0005] Phenotypic screening identified some of the compounds known in the literature to be PDE3 inhibitors to be useful for the treatment of certain cancers. Co-expression of PDE3A and/or PDE3B and Schlafen 12 (SLFN12) polynucleotides or polypeptides are typically required for cells to be sensitive. PDE3A/B inhibitors which cause drug sensitivity have been found to stabilze the formation of a complex between PDE3A or PDE3B and SLFN12. PDE3A/B inhibitors which do not cause cell sensitivity typically do not stabilize the PDE3A- or PDE3B-SLFN12 complex.

[0006] Several PDE-3 inhibitors such as milrinone, cilostazol, and levosimendan have been approved for clinical treatment of cardiovascular indications or thrombocythemia (anagrelide), but not for cancer indication. The most recent quality review of PDE inhibitors (Nature Reviews Drug Discovery 13, 290-314, (2014)) barely mentions cancer. From WO 2014/164704, WO2017/027854, and WO2017/134231 some PDE3 inhibitors are known.

[0007] Especially the cardiac mode of action mediated unwanted effects of PDE-3 inhibitors (Movsesian &Kukreja, S. H. Francis et al. (eds.), Phosphodiesterases as Drug Targets, Handbook of Experimental Pharmacology 204, 2011; p 237ff) may limit their therapeutic use when PDE3-inhibiting agents are used on a short- or/and long term basis, e.g. in cancer patients and a suitable therapeutic window is needed.

[0008] Some dihydrooxydiazinones are known, however, the state of the art does not describe the dihydrooxadiazinone compounds of general formula (I) of the present invention as described and defined herein.

SUMMARY

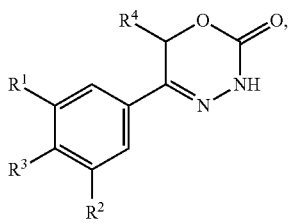
[0009] It has now been found, and this constitutes at least in part one basis of the present invention, that the compounds of the present invention have surprising and advantageous properties.

[0010] In particular, the compounds of the present invention have surprisingly been found to inhibit tumor cell proliferation with IC_{50} values of <100 nM in e.g. HeLa cells. Additionally, the compounds require higher concentrations for PDE3A and/or PDE3B inhibition where IC_{50} values for enzymatic PDE3A and/or PDE3B inhibition may be >2.5 times higher than IC_{50} values for tumor cell proliferation. Without wishing to be bound by theory, this distinction in inhibitory properties may be associated with PDE3A-SLFN12 complex induction and/or improved pharmacokinetic parameters in vitro or in vivo and/or improved physicochemical properties and/or improved safety pharmacological properties. With these advantageous properties, the compounds described herein may therefore be used for the treatment or prophylaxis of hyperproliferative diseases, such as cancer diseases.

[0011] The present invention provides compounds of general formula (I) which modulate formation of a PDE3A- and/or PDE3B-SLFN12 complex, methods for their preparation, pharmaceutical composition and the use thereof and methods of treatment or prophylaxis of diseases, in particular of hyperproliferative diseases more particularly of cancer diseases. These and other features of the present teachings are set forth herein.

[0012] In accordance with a first aspect, the present invention provides compounds of general formula (I):

formula (I)



where

[0013] R^1 is selected from a hydrogen atom, a halogen atom, a cyano group, a C_1-C_3-alkyl group, a C_1-C_3-haloalkyl group, and a C_1-C_3-haloalkoxy group;